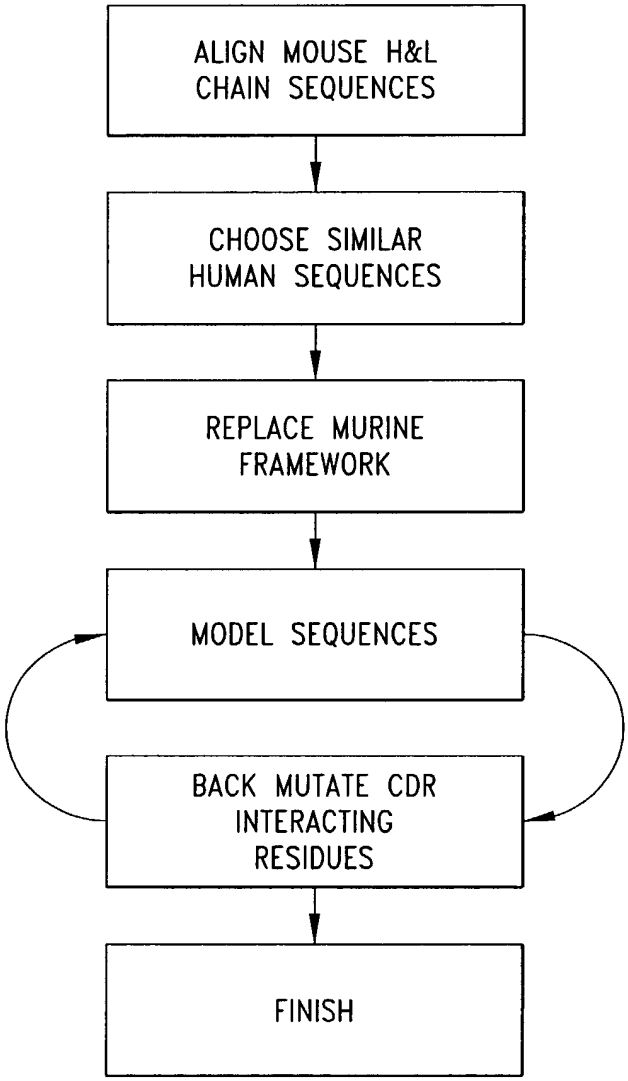


Fig. 1

NR-LU-13 Heavy chain variable region sequences

```
GAG GTT CAG CTG CAG CAG TCT GGG GCA GAG CTT GTG AAG CCA GGG GCC TCA GTC AGG TTG TCC TGC
Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Arg Leu Ser Cys   22
                                CDR1
ACA GCT TCT GGC TTC AAC ATT AAA GAC ACC TAT ATG CAC TGG GTG ATA GAG AGG CCT GAA CAG GGC
Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr Tyr Met His Trp Val Ile Glu Arg Pro Glu Gln Gly   44
                                    CDR2
CTG GAG TGG ATT GGA AGG ATT GAT CCT GCG AAT GGT AAT ACT AAA TGT GAC CCG AAG TTC CAG GGC
Leu Glu Trp Ile Gly Arg Ile Asp Pro Ala Asn Gly Asn Thr Lys Cys Asp Pro Lys Phe Gln Gly   66

AAG GCC ACT ATA ACA GCA GAC ACA TCC TCC AAC ACA GCC TAC CTG CAG CTC AGC AGC CTG ACA TCT
Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr Leu Gln Leu Ser Ser Leu Thr Ser   88
                                                CDR3
GAG GAC ACT GCC GTC TAT TAC TGT TCT AGA GAG GTC CTA ACT GGG ACG TGG TCT TTG GAC TAC TGG
Glu Asp Thr Ala Val Tyr Tyr Cys Ser Arg Glu Val Leu Thr Gly Thr Trp Ser Leu Asp Tyr Trp  110

GGT CAA GGA ACC TCA GTC ACC GTC TCC TCA
Gly Gln Gly Thr Ser Val Thr Val Ser Ser                                                  120
```

NR-LU-13 Light chain variable region sequences

```
GAC ATC CAG ATG ATT CAG TCT CCA TCG TCC ATG TTT GCC TCT CTG GGA GAC AGA GTC AGT CTC TCT
Asp Ile Gln Met Ile Gln Ser Pro Ser Ser Met Phe Ala Ser Leu Gly Asp Arg Val Ser Leu Ser   22
                        CDR1
TGT CGG GCT AGT CAG GGC ATT AGA GGT AAT TTA GAC TGG TAT CAG CAG AAA CCA GGT GGA ACT ATT
Cys Arg Ala Ser Gln Gly Ile Arg Gly Asn Leu Asp Trp Tyr Gln Gln Lys Pro Gly Gly Thr Ile   44
                            CDR2
AAA CTC CTG ATC TAC TCC ACA TCC AAT TTA AAT TCT GGT GTC CCA TCA AGG TTC AGT GGC AGT GGG
Lys Leu Leu Ile Tyr Ser Thr Ser Asn Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly   66

TCT GGG TCA GAT TAT TCT CTC ACC ATC AGC AGC CTA GAC TCT GAA GAT TTT GCA GAC TAT TAC TGT
Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Asp Ser Glu Asp Phe Ala Asp Tyr Tyr Cys   88
                    CDR3
CTA CAG CGT AAT GCG TAT CCG TAC ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA
Leu Gln Arg Asn Ala Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys              107
```

Fig. 2

Light Chain

1				5					10
ASP	ILE	GLN	MET	**THR**	GLN	SER	PRO	SER	SER
11				15					20
LEU	**SER**	ALA	SER	**VAL**	GLY	ASP	ARG	VAL	**THR**
21				25					30
ILE	THR	CYS	ARG	ALA	SER	GLN	GLY	ILE	ARG
31				35					40
GLY	ASN	LEU	ASP	TRP	TYR	GLN	GLN	LYS	PRO
41				45					50
GLY	**LYS**	**GLY**	**PRO**	LYS	LEU	LEU	ILE	TYR	SER
51				55					60
THR	SER	ASN	LEU	ASN	SER	GLY	VAL	PRO	SER
61				65					70
ARG	PHE	SER	GLY	SER	GLY	SER	GLY	SER	ASP
71				75					80
TYR	**THR**	LEU	THR	ILE	SER	SER	LEU	**GLN**	**PRO**
81				85					90
GLU	ASP	PHE	ALA	**THR**	TYR	TYR	CYS	LEU	GLN
91				95					100
ARG	ASN	ALA	TYR	PRO	TYR	THR	PHE	GLY	**GLN**
101				105					
GLY	THR	LYS	LEU	GLU	ILE	LYS			

The humanized sequence of NRX451 light chain, residue positions which differ between NR-LU-13 and NRX451-humanized are marked with bold type.

Fig. 3

Heavy Chain

1				5					10
GLN	VAL	GLN	LEU	**VAL**	GLN	SER	GLY	ALA	GLU
11				15					20
VAL	**LYS**	LYS	PRO	GLY	ALA	SER	VAL	**LYS**	**VAL**
21				25					30
SER	CYS	**LYS**	ALA	SER	GLY	PHE	ASN	ILE	LYS
31				35					40
ASP	THR	TYR	MET	HIS	TRP	VAL	**ARG**	**GLN**	**ALA**
41				45					50
PRO	**GLY**	GLN	GLY	LEU	**GLN**	TRP	**MET**	GLY	ARG
51				55					60
ILE	ASP	PRO	ALA	ASN	GLY	ASN	THR	LYS	CYS
61				65					70
ASP	**LEU**	**SER**	PHE	GLN	GLY	**ARG**	**VAL**	THR	ILE
71				75					80
THR	ALA	ASP	THR	SER	**ILE**	ASN	THR	ALA	TYR
81				85					90
MET	**GLU**	LEU	SER	SER	LEU	**ARG**	SER	**ASP**	ASP
91				95					100
THR	ALA	VAL	TYR	TYR	CYS	SER	ARG	GLU	VAL
101				105					110
LEU	THR	GLY	THR	TRP	SER	LEU	ASP	TYR	TRP
111				115					120
GLY	GLN	GLY	THR	**LEU**	VAL	THR	VAL	SER	SER

The humanized sequence of NRX451 light chain, residue positions which differ between NR-LU-13 and NRX451-humanized are marked with bold type.

Fig. 4

Alignment of the Light Chain Variable Regions of NR-LU-13 (top) and humanized NRX451 (bottom).

```
DIQMISSPSSMFASLGDRVSLSC RASQGIRGNLD WYQQKPGGTIKLLIY STSNLNS
.... ..... .. .... . ........... ....... ..... .......
DIQMTQSPSSLSASVGDRVTITC RASQGIRGNLD WYQQKPGKGPKLLIY STSNLNS
                        CDR1                        CDR2

GVPSRFSGSGSGSDYSLTISSLESEDFADYYC LQRNAYPYTF GGGTKLEIK
.............. ..... .... ... .......... . .......
GVPSRFSGSGSGSDYTLTISSLQPEDFATYYC LQRNAYPYTF GQGTKLEIK
                                  CDR3
```

Alignment of the Heavy Chain Variable Regions of NR-LU-13 (top) and humanized NRX451 (bottom).

```
EVQLQQSGAELVKPGASVRLSCTASGFNIK DTYMH WVIERPEQGLEWIG
 ... ..... ..... .. ....... ..... .. . ... . .
QVQLVQSGAEVKKPGASVKVSCKASGFNIK DTYMH WVRQAPGQGLQWMG
                               CDR1

RIDPANGNTK CDPKFQGKATITADTSSNTAYLQLSSLTSEDTAVYYCS
.......... .. ... ....... .... .... . ........
RIDPANGNTK CDLSFQGRVTITADTSINTAYMELSSLRSDDTAVYYCS
  CDR2

REVLTGTWSLDY WGQGTSVTVSS
............ ..... .....
REVLTGTWSLDY WGQGTLVTVSS
  CDR3
```

Fig. 5

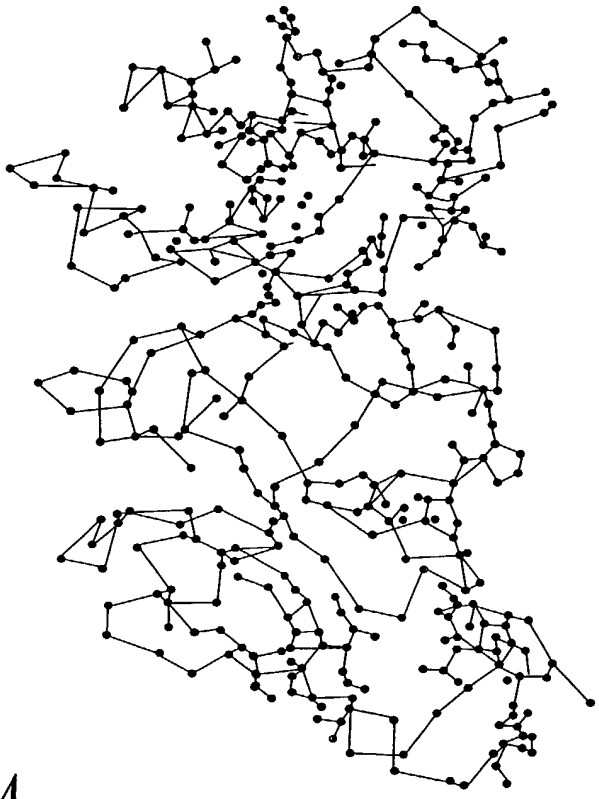


Fig. 6A

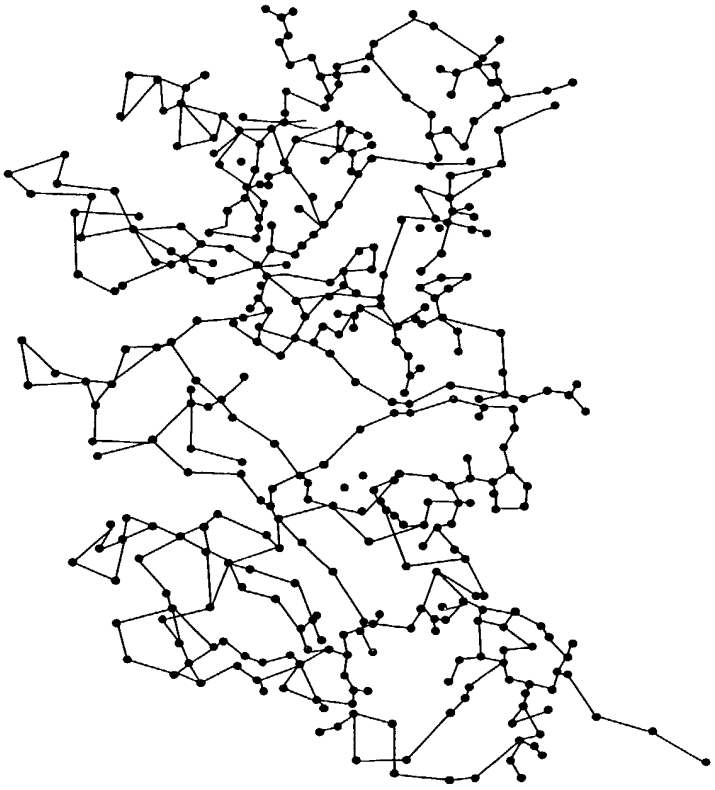


Fig. 6B

Same frequencies, but matching with human sequences. Only one occurence of Asp at poition 182 is found and no occurences of Cys at position 181.

RES	181	182
A	-	0.48
R	-	0.02
N	0.01	0.18
D	0.00	0.00
C	0.00	0.00
Q	0.00	-
E	-	-
G	0.00	0.01
H	0.00	-
I	-	0.00
L	-	0.00
K	0.00	0.00
M	-	-
F	0.03	-
P	0.00	0.01
S	0.01	0.23
T	-	0.02
W	0.00	-
Y	0.91	-
V	0.00	0.02
X	0.01	0.02
0	-	-
-	-	-
Z	-	-
B	-	0.00
Total	1.00	1.00

Fig. 7A

Sequence positions 50 and 183 are structural mutations within 5 A of the CDR's. Frequency of residue types at these positions are identical.

Position 50 (153 human lambda sequences)

RES	50
A	-
R	-
N	-
D	-
C	-
Q	-
E	-
G	-
H	-
I	0.00
L	-
K	-
M	0.00
F	-
P	0.93
S	-
T	-
W	-
Y	-
V	-
X	0.06
O	-
-	-
Z	-
B	-
Total	1.00

Fig. 7B

Position 50 (279 human kappa sequences)

RES	50
A	0.00
R	-
N	-
D	-
C	-
Q	-
E	-
G	-
H	-
I	0.00
L	0.00
K	-
M	-
F	-
P	0.96
S	-
T	-
W	-
Y	-
V	-
X	0.03
0	-
-	-
Z	-
B	-
Total	1.00

Fig. 7C

Position 50 is highly conserved in all the sequences, but proline can be exchanged by Ile or Leu. The framework used for the light chain (6fab) does have an Ile at this position. If this position is compared to other structures the backbone torsions are the same for structures with a Pro and an Ile at this position.

Position 50 (153 human lambda sequences)

RES	183
A	0.06
R	-
N	0.00
D	0.21
C	-
Q	0.15
E	0.01
G	0.01
H	-
I	0.00
L	0.00
K	0.00
M	-
F	0.00
P	0.40
S	0.01
T	0.01
W	-
Y	0.00
V	0.08
X	0.02
0	-
-	-
Z	-
B	0.00
Total	1.00

Fig. 7D

Position 183 (1210 mouse sequences)

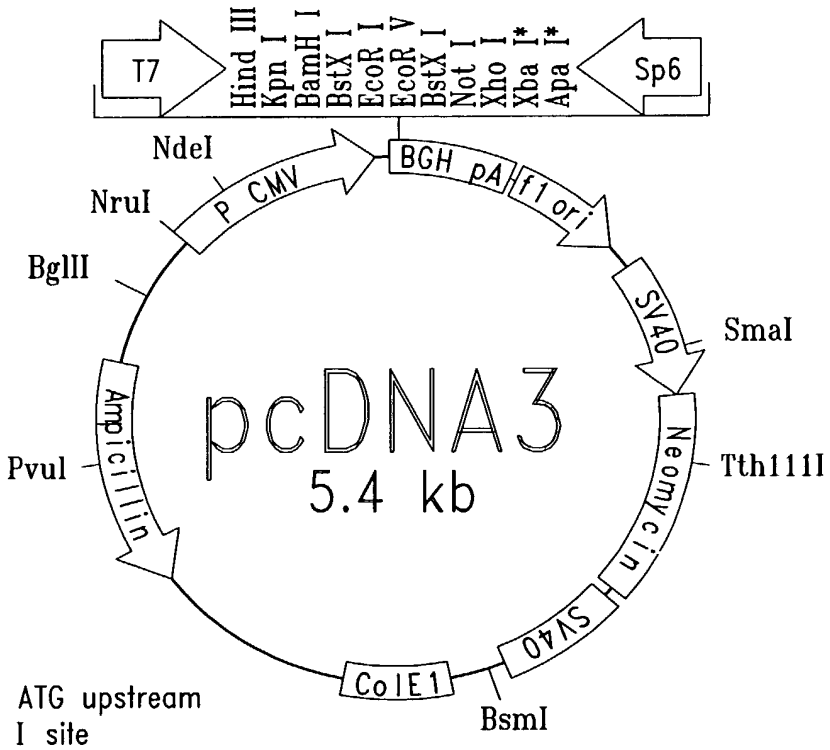
RES	183
A	0.16
R	0.00
N	0.00
D	0.13
C	-
Q	0.16
E	0.25
G	0.02
H	0.00
I	-
L	-
K	0.00
M	-
F	-
P	0.17
S	0.08
T	0.00
W	-
Y	-
V	0.00
X	0.02
0	-
-	-
Z	-
B	-
Total	1.00

Leu is seen in human sequences at this position, but never in murine sequences, for both human and murine Sequences P is the most frequently occuring residue at position 183.

Fig. 7E

Comments for pcDNA3:
5446 nucleotides

CMV promotor: bases 209-863
T7 promotor: bases 864-882
Polylinker: bases 889-994
Sp6 promotor: bases 999-1016
BGH poly A: bases 1018-1249
SV40 promotor: bases 1790-2115
SV40 origin of replication: bases 1984-2069
Neomycin ORF: bases 2151-2945
SV40 poly A: bases 3000-3372
ColE1 origin: bases 3632-4305
Ampicillin ORF: bases 4450-5310



*There is a ATG upstream of the Xba I site

Fig. 8

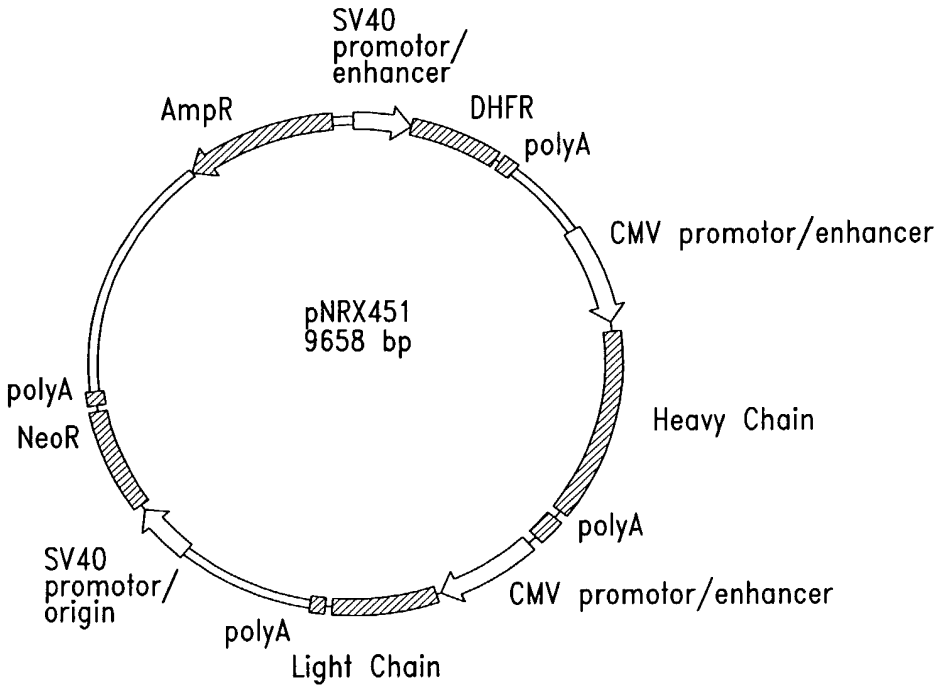


Fig. 9

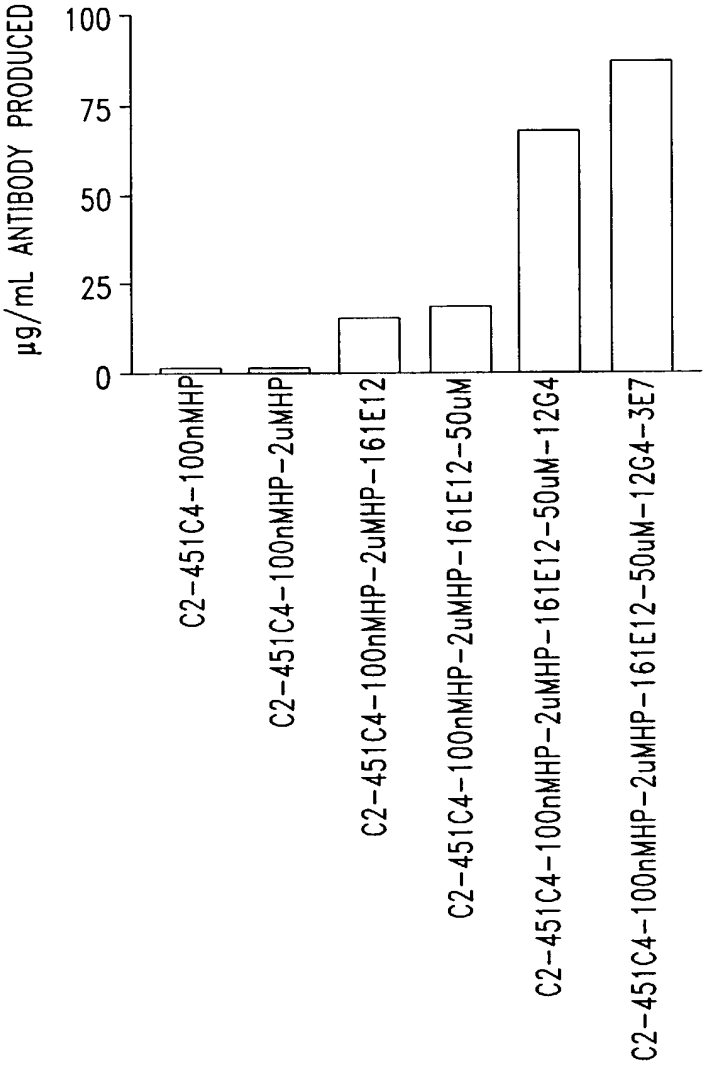


Fig. 10

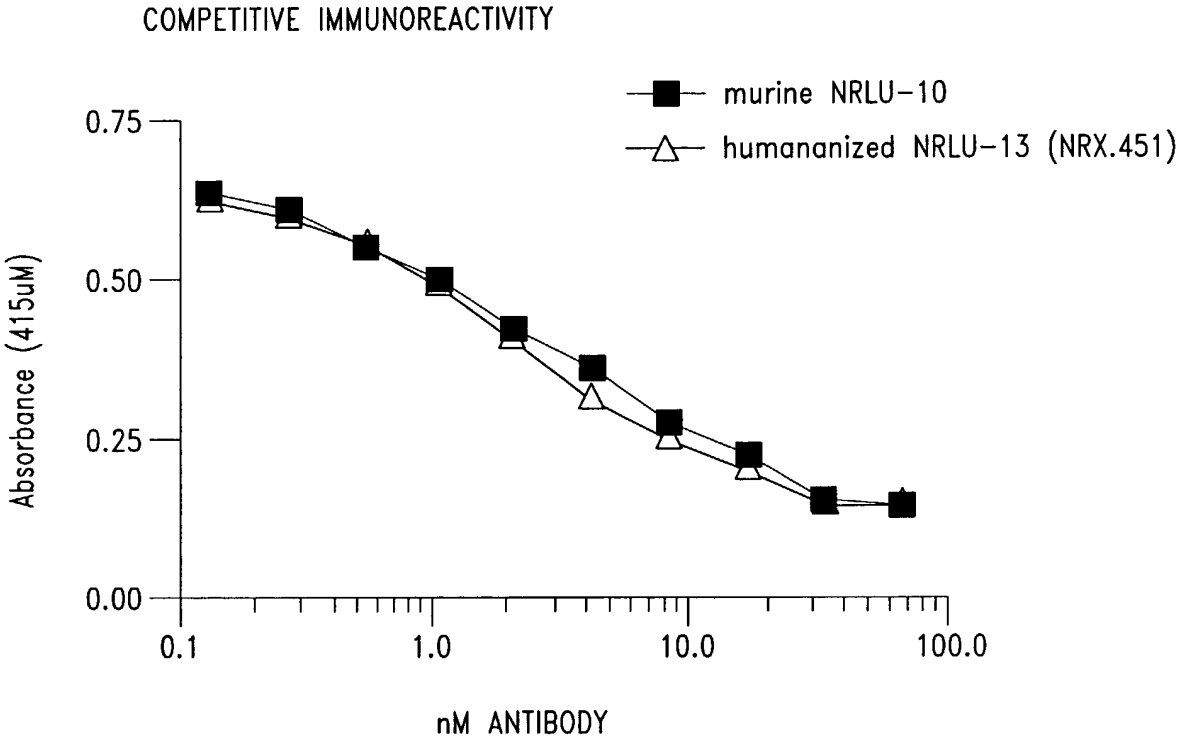


Fig. 11

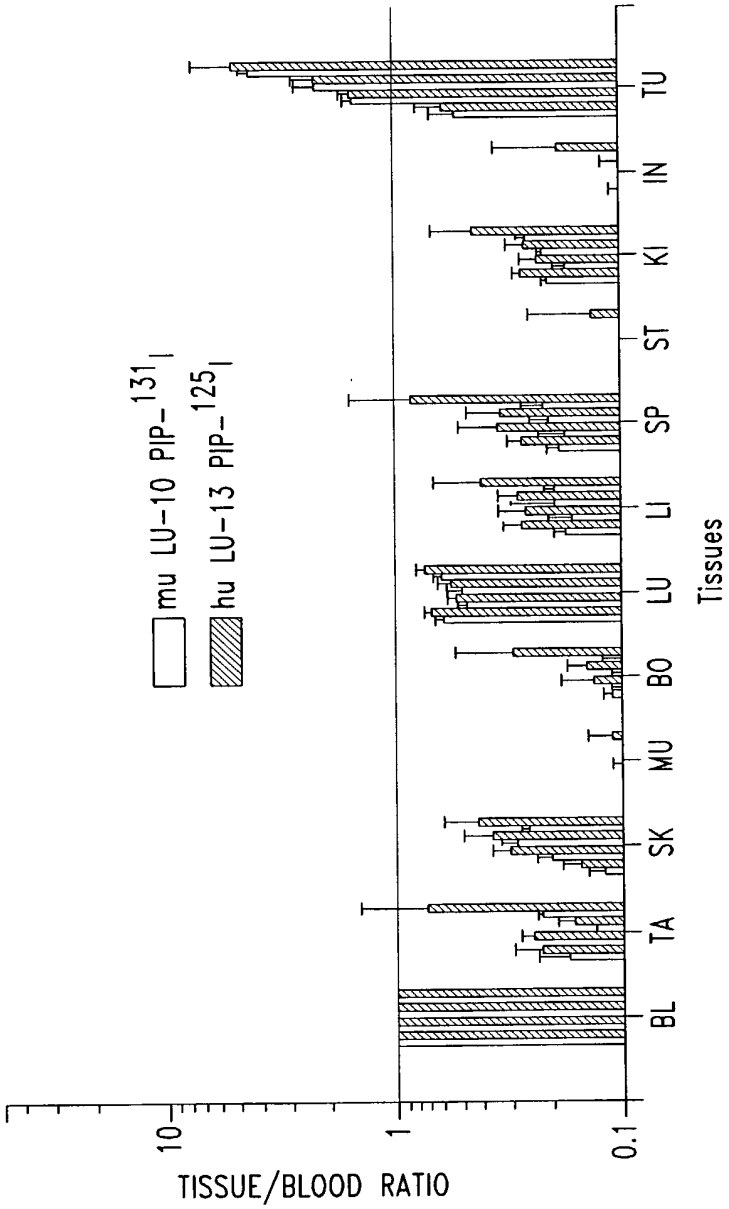


Fig. 12

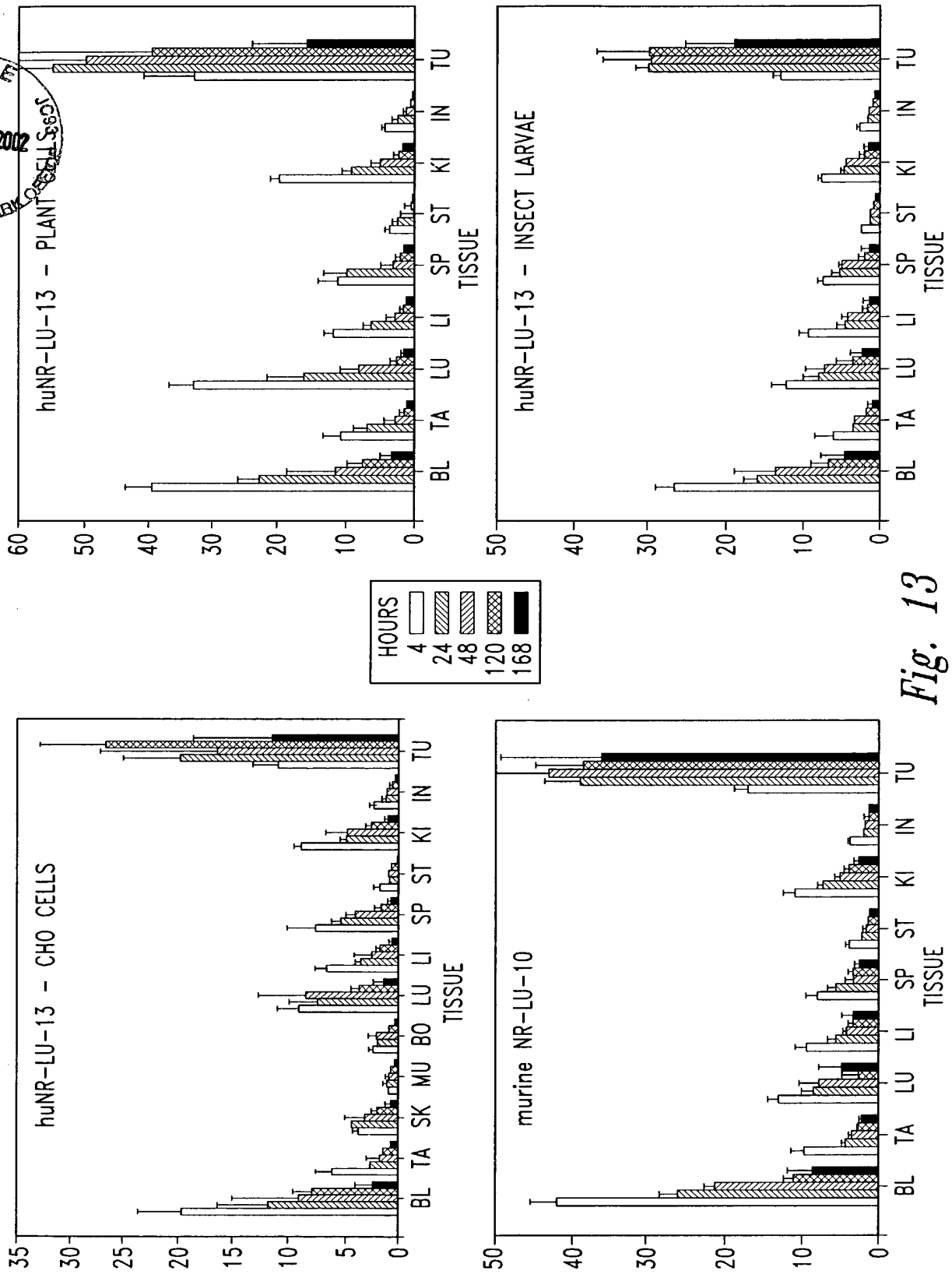


Fig. 13

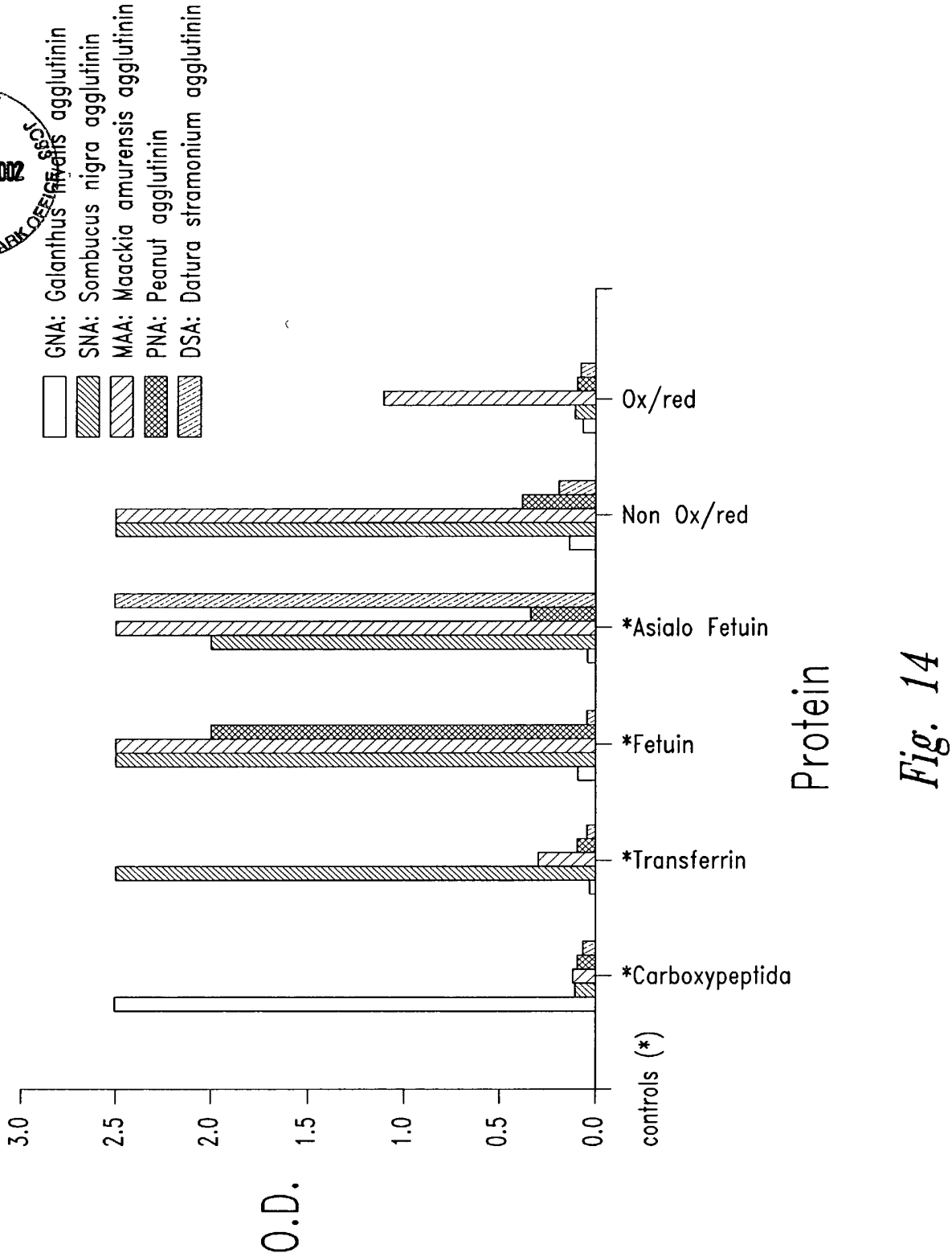


Fig. 14

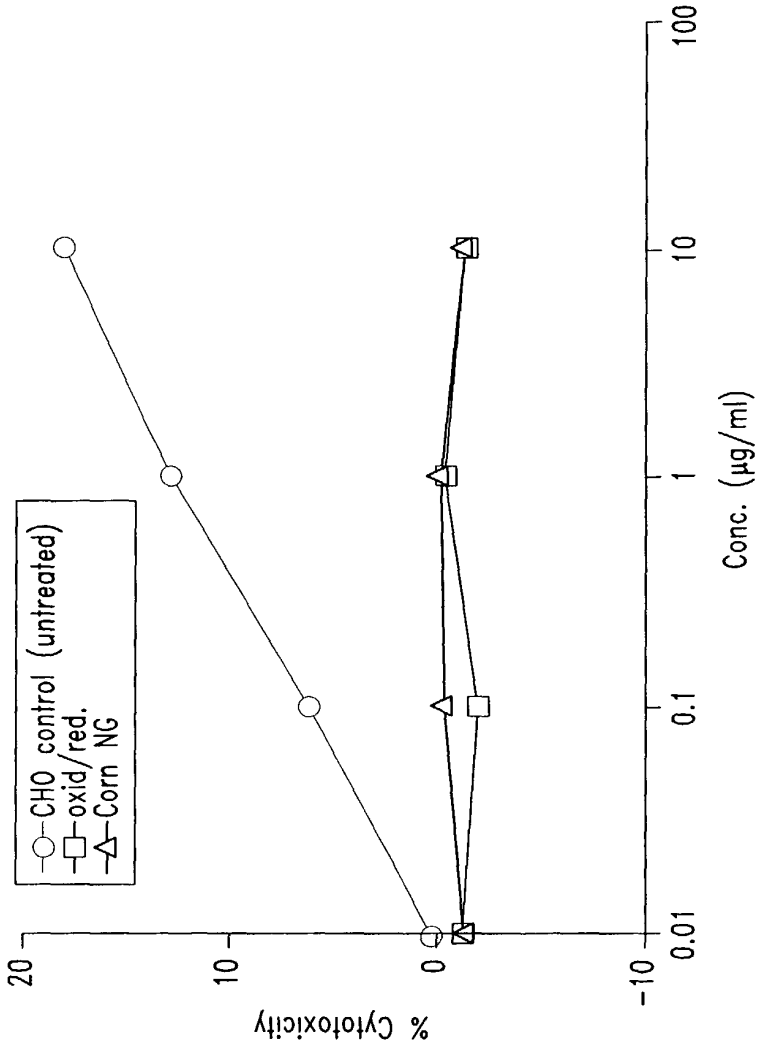


Fig. 15A

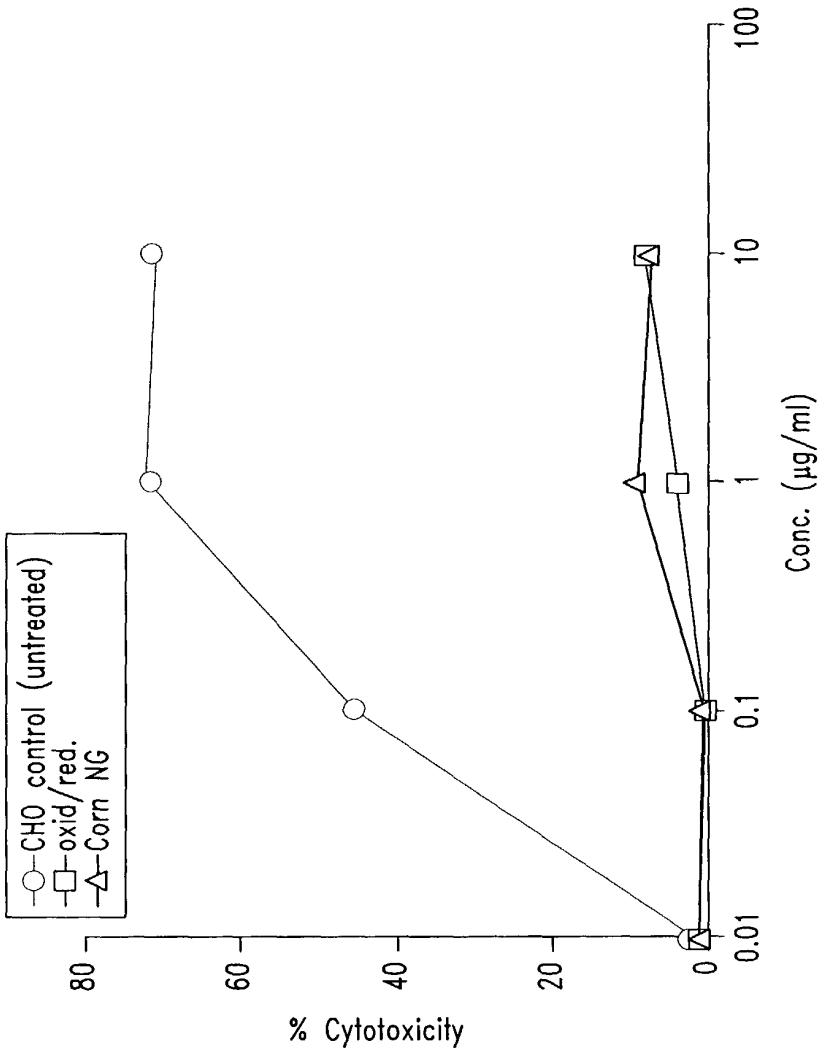


Fig. 15B

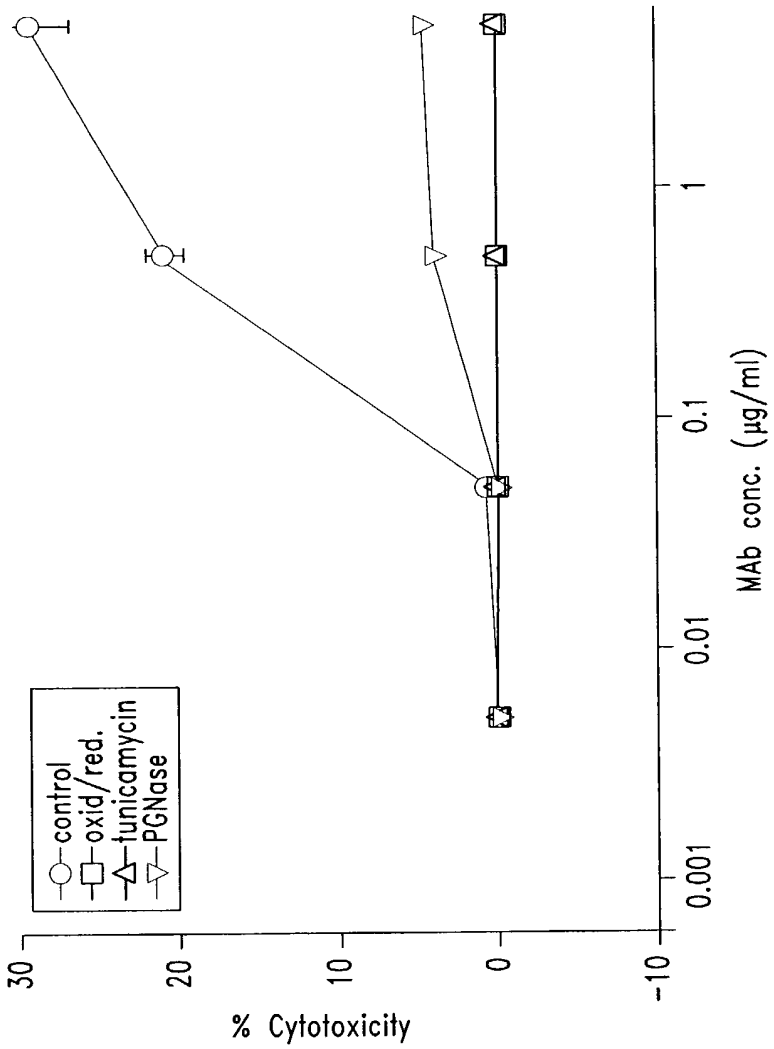


Fig. 15C

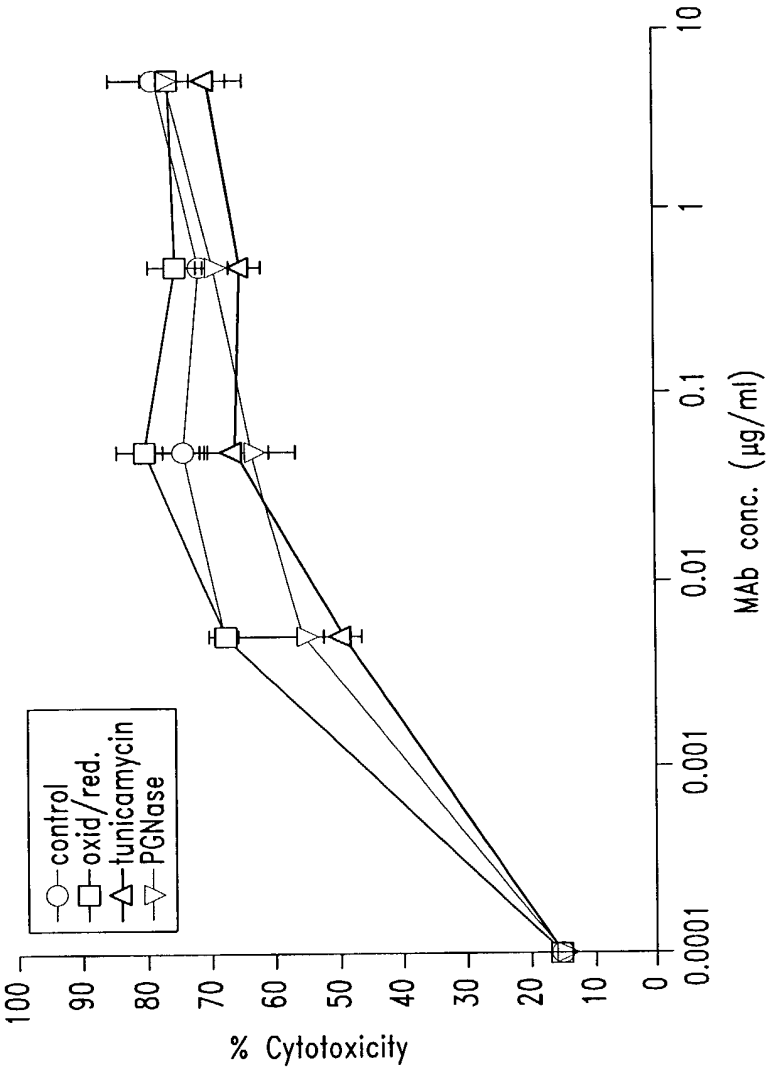


Fig. 15D

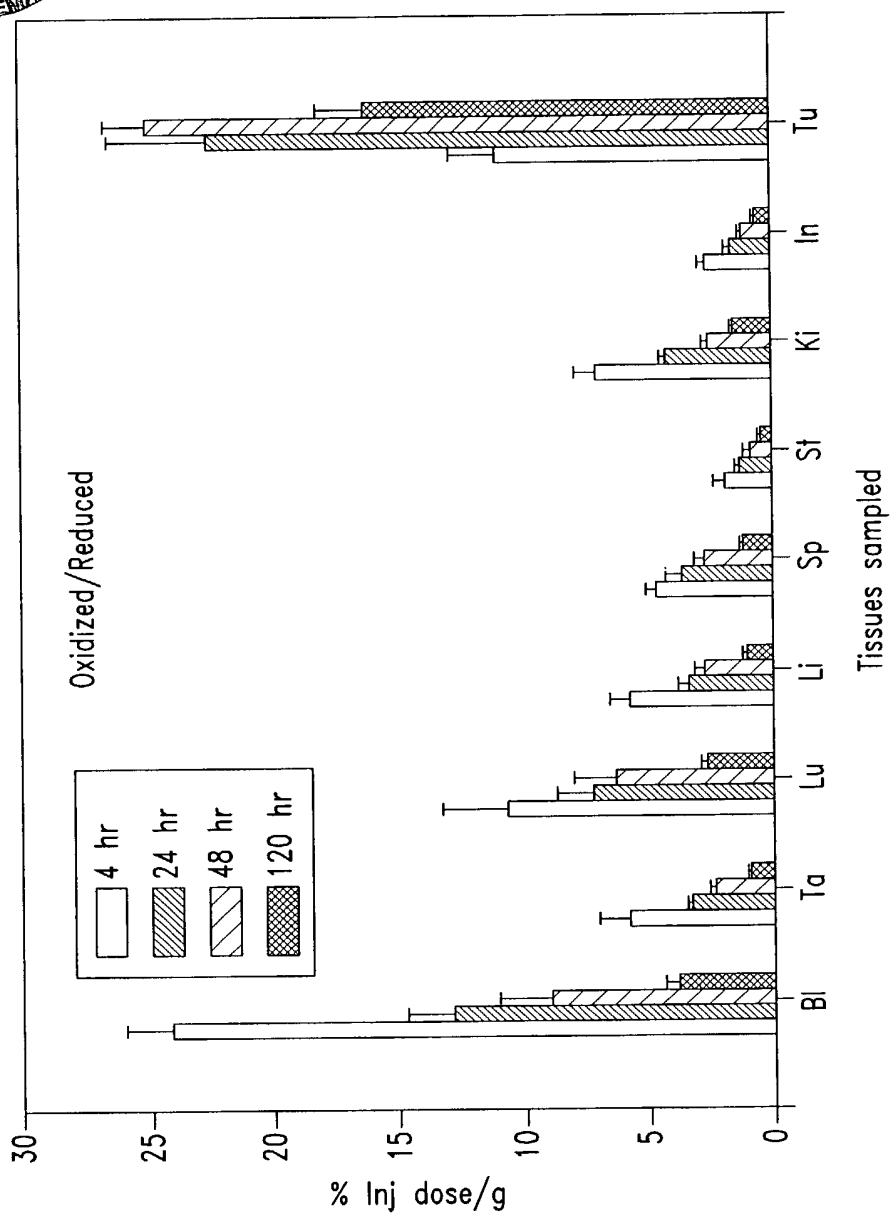


Fig. 16A

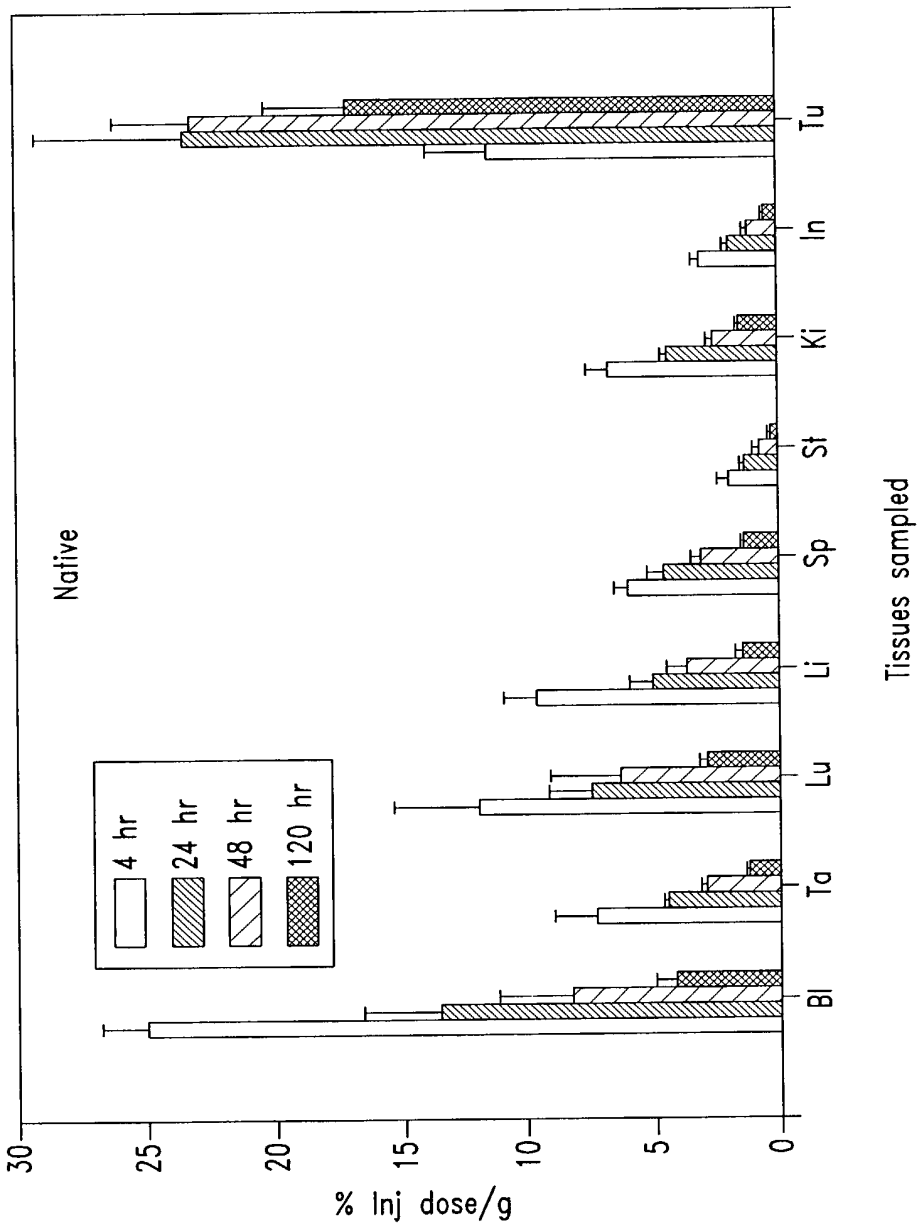


Fig. 16B

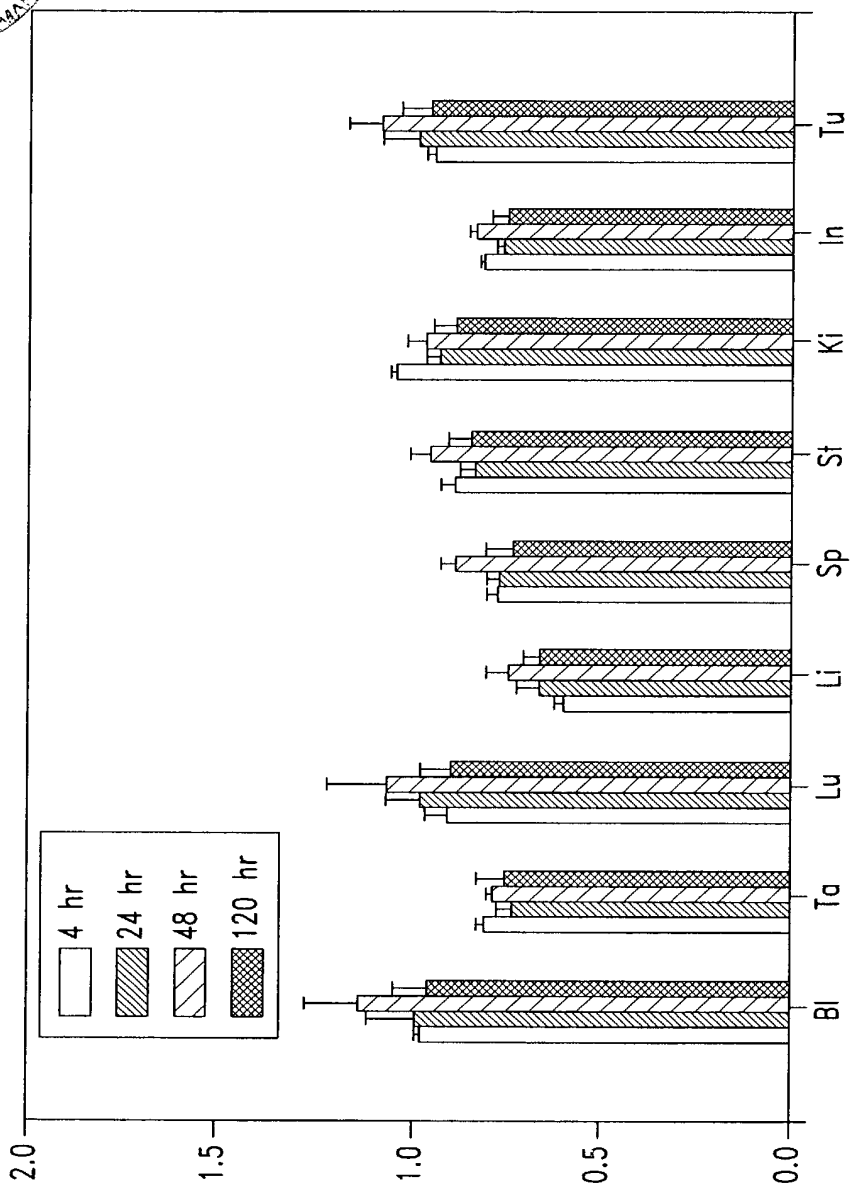


Fig. 16C

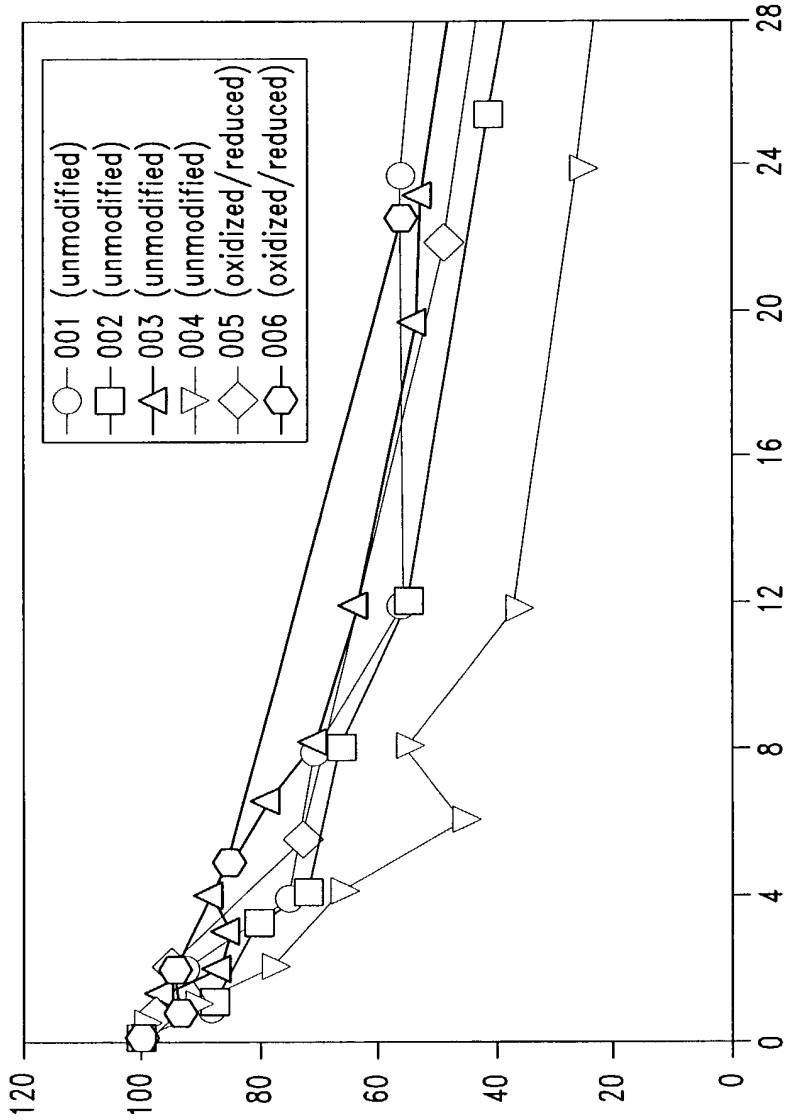


Fig. 17

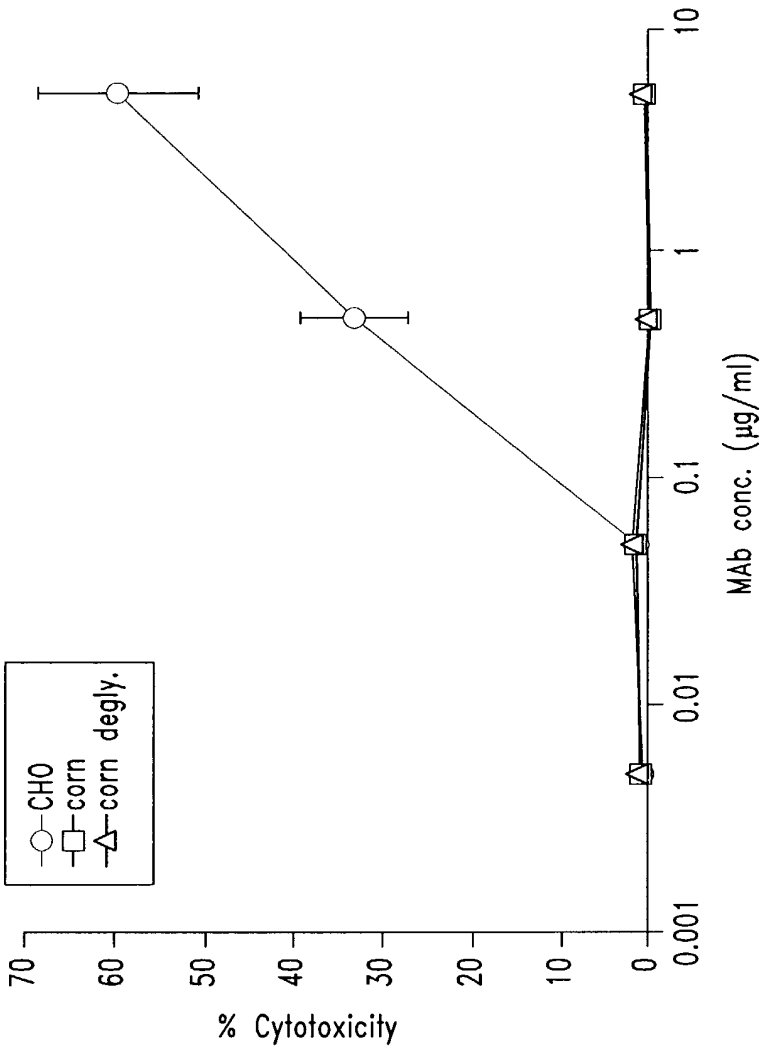


Fig. 18

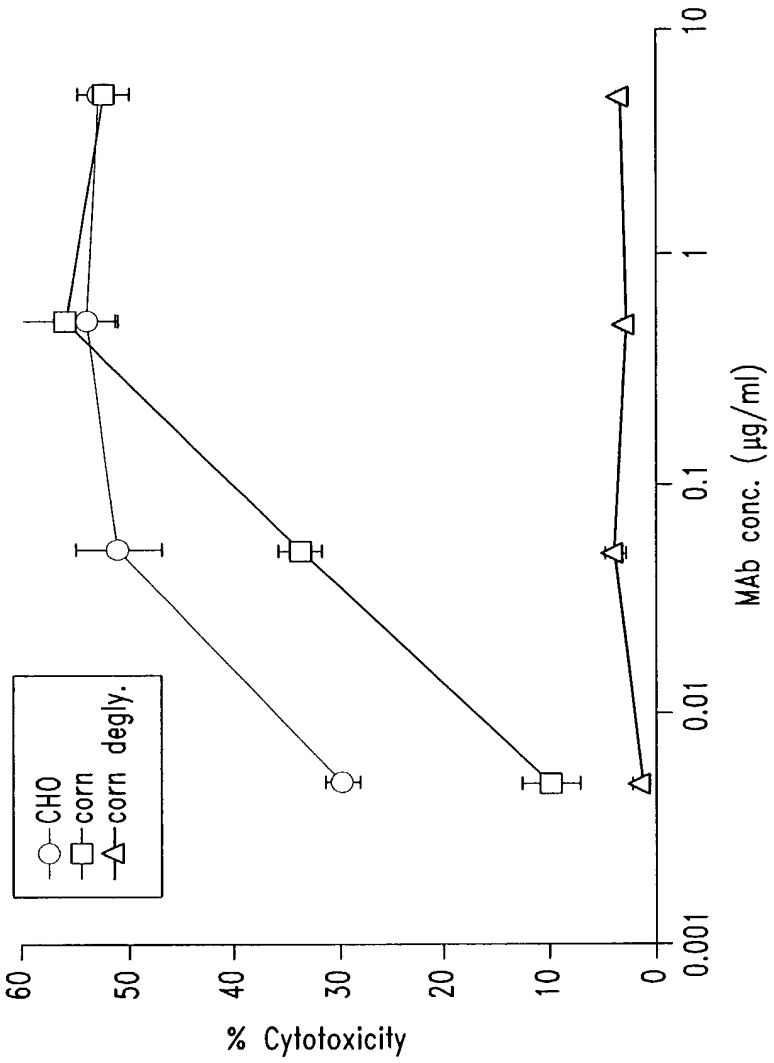


Fig. 19

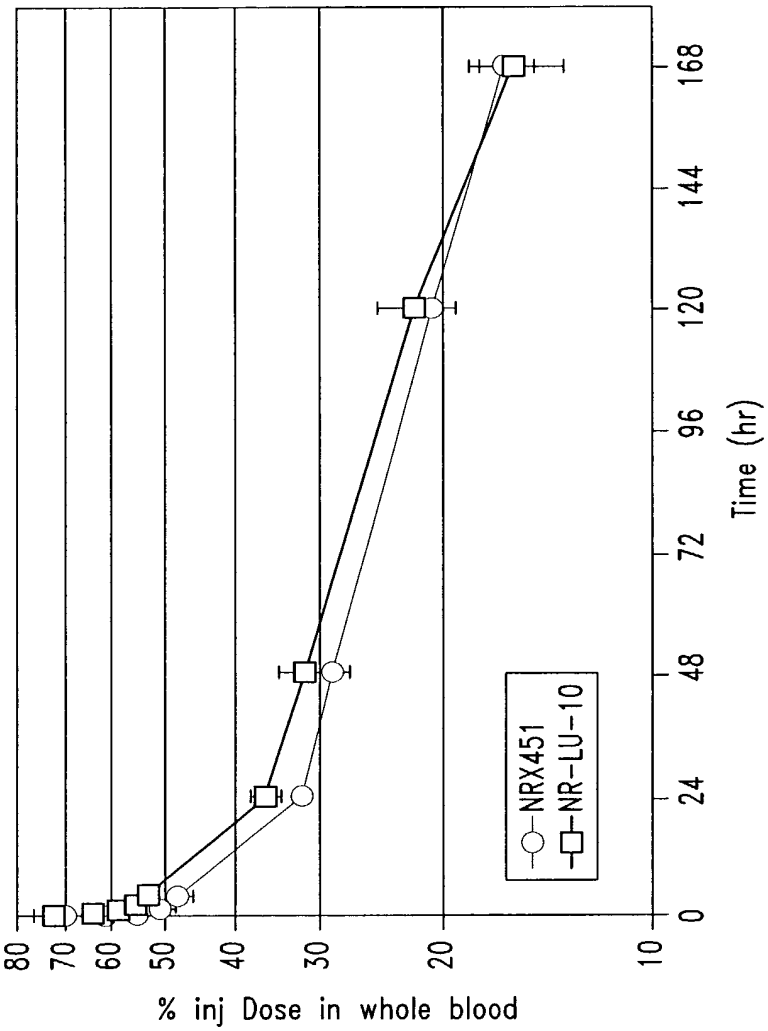


Fig. 20

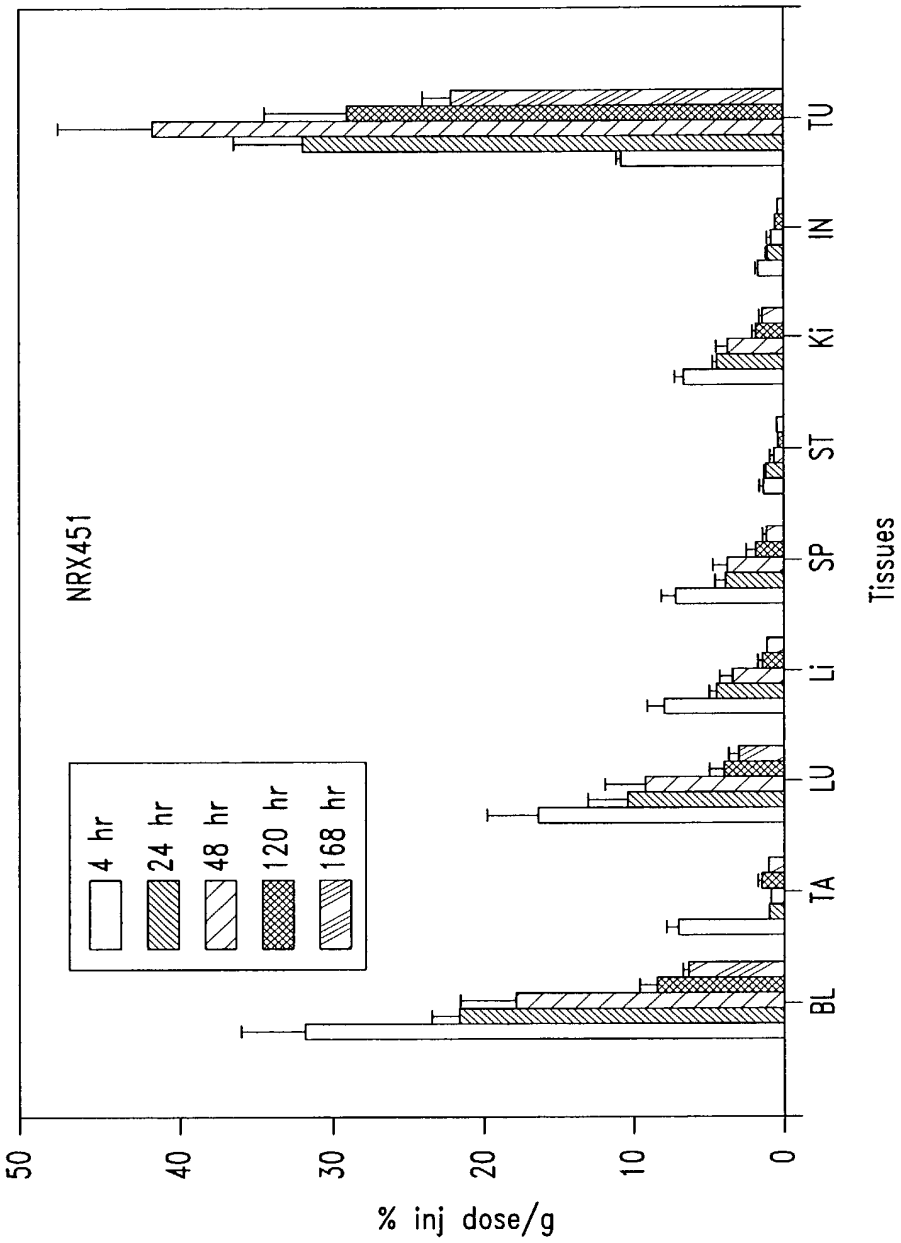


Fig. 21A

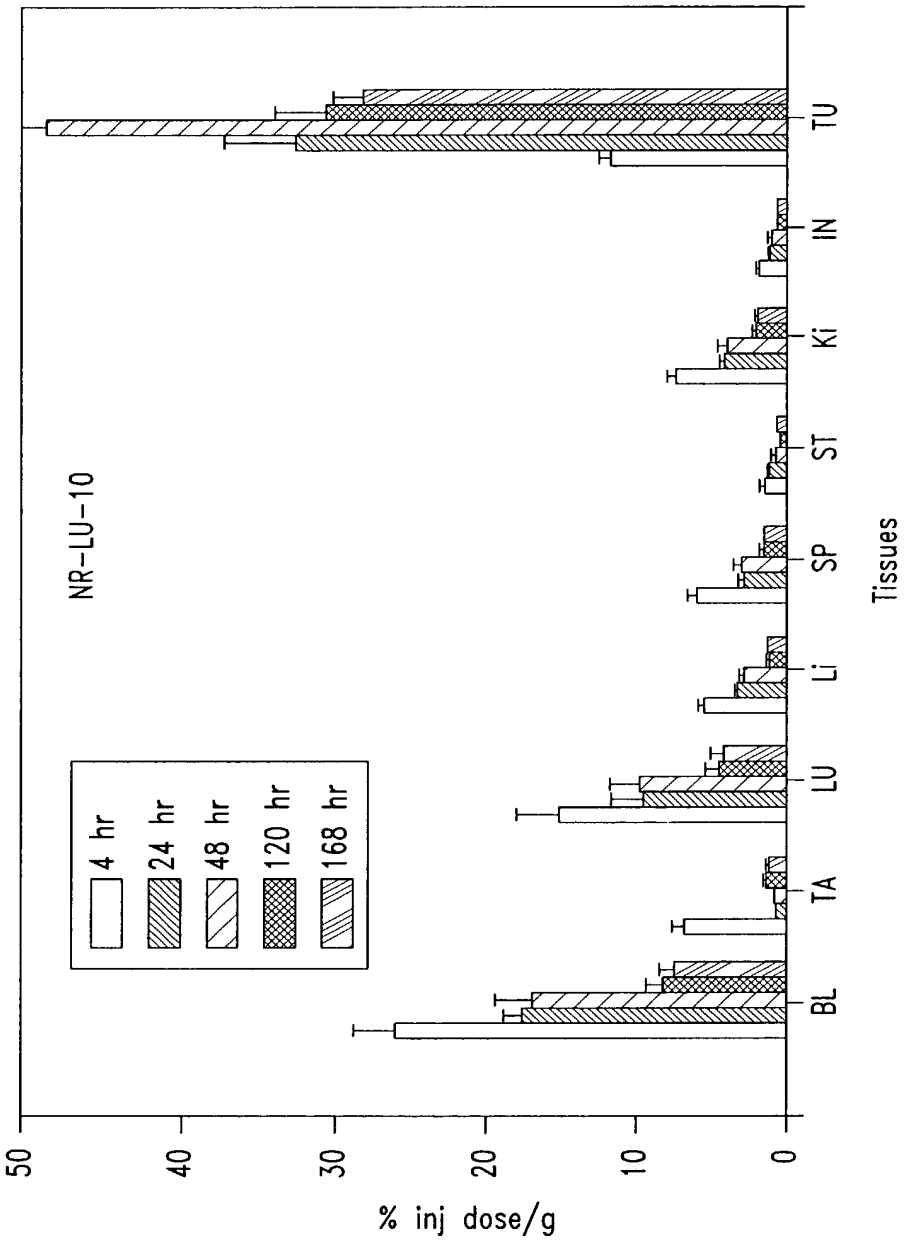
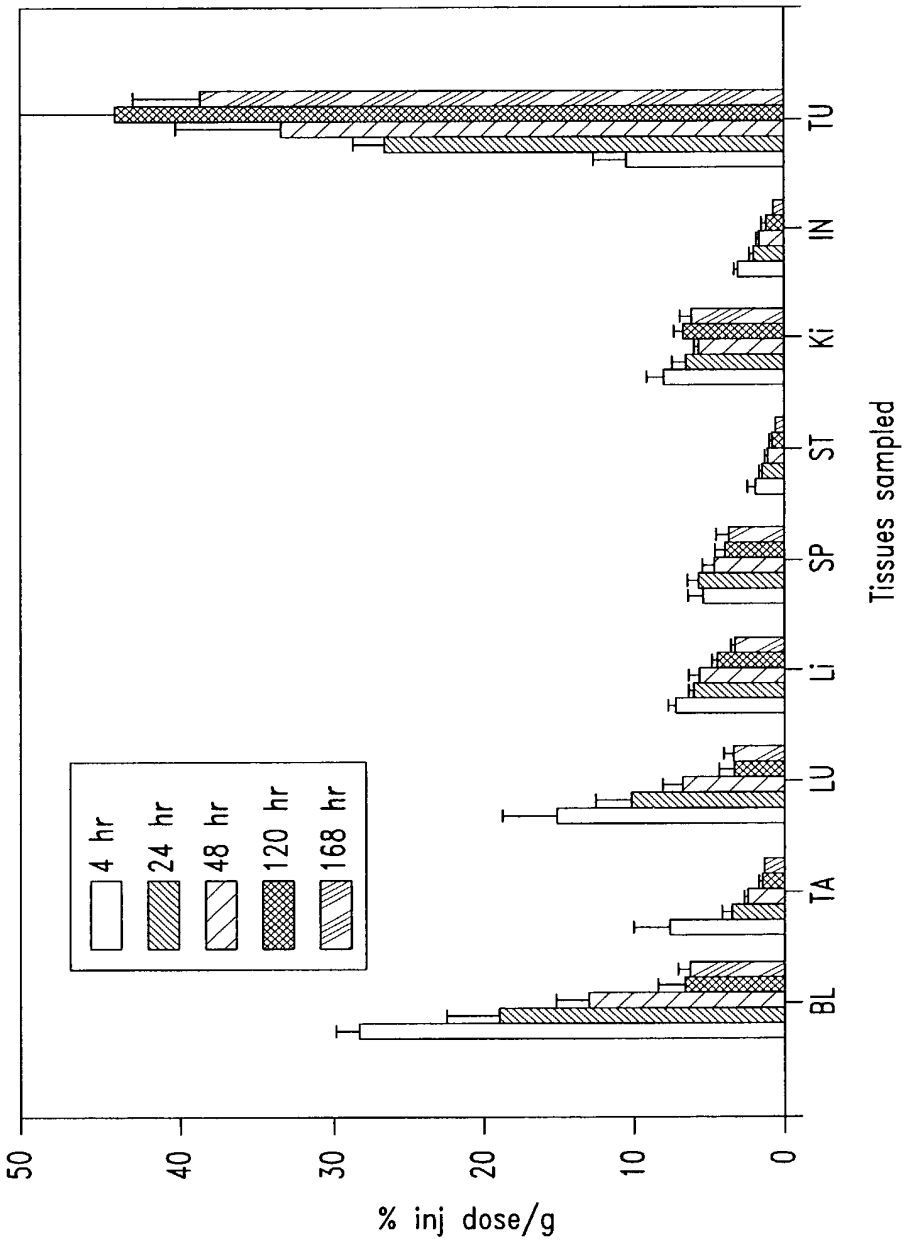


Fig. 21B



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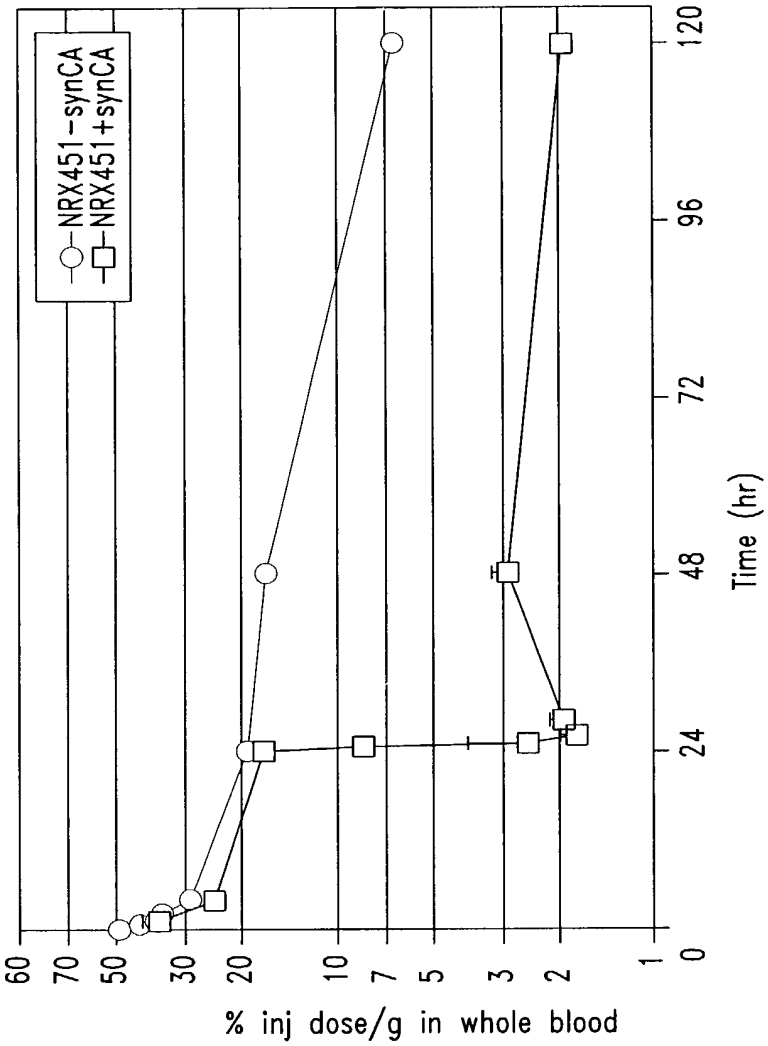

Fig. 23

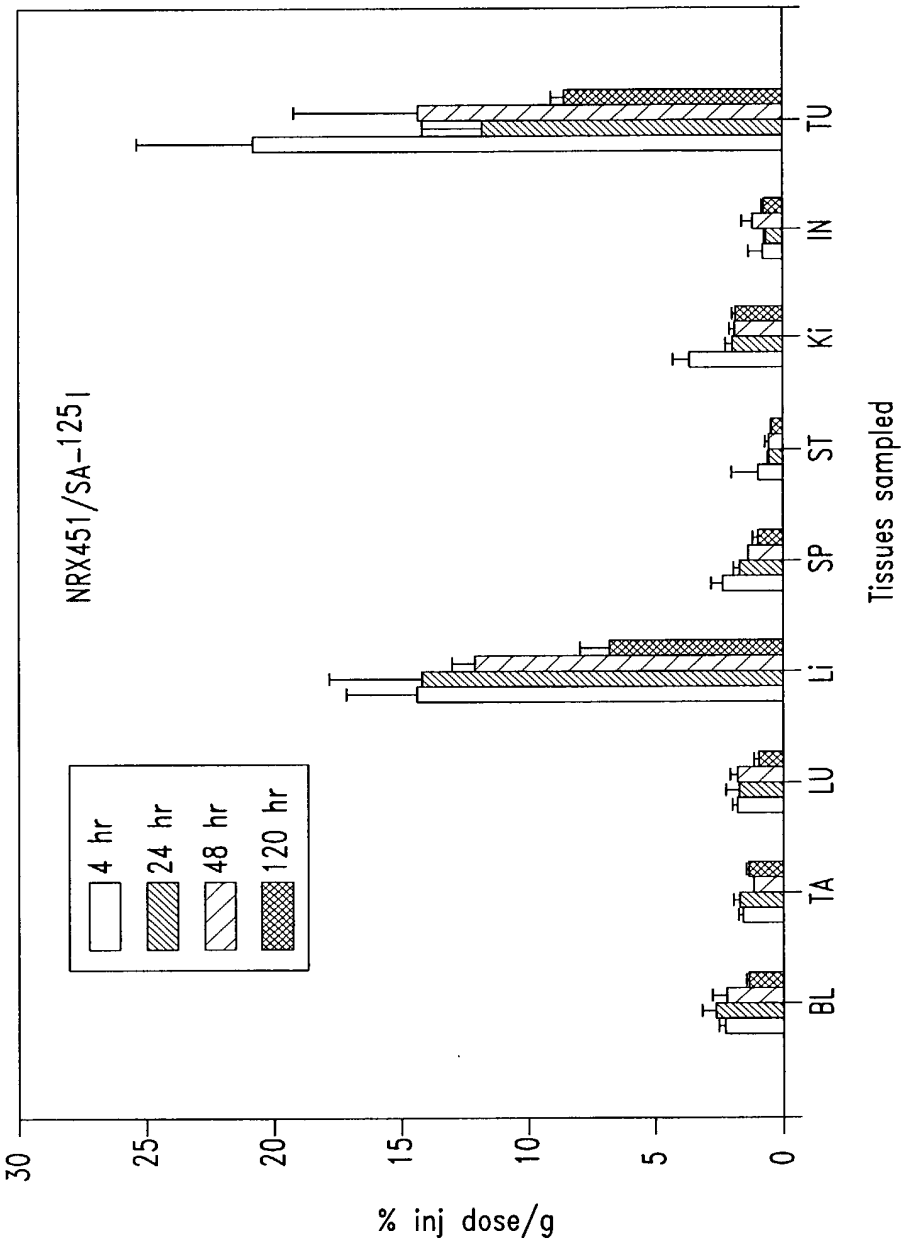

Fig. 24A

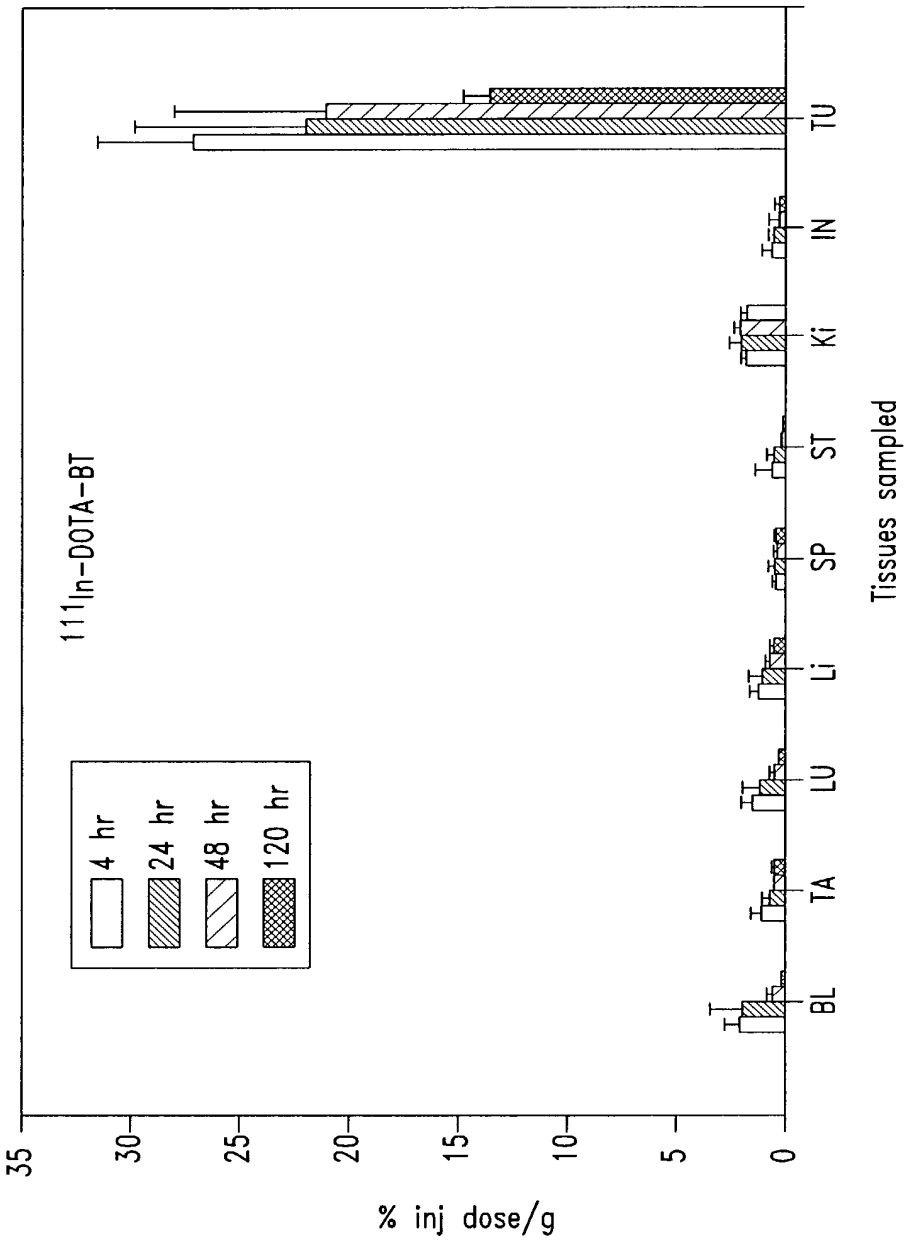

Fig. 24B